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Cerebral edema.

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Two major types of brain edema may be discriminated, characterized by intra- or extracellular fluid accumulation. Intracellular (cytotoxic) edema is found after cerebral ischemia, trauma, intoxications, and metabolic disorders. Pathogenetic mechanisms include (1) failure of active Na+ export via Na/K-ATPase because of energy shortage, (2) increased Na+-permeability, or (3) activation of Na+-driven membrane pumps. The latter mechanism reflects homeostatic functions of astroglia, which at reduced availability of energy resources uses the remaining Na+-gradient to fuel uptake of transmitters such as glutamate, and for control of pH(i). Extracellular (vasogenic) edema is caused by damage to the blood-brain barrier and consists of protein-rich fluid. It accompanies brain tumors, trauma, infections, and hypertensive crisis. Pathogenetic mechanisms include (1) opening of tight junctions responsible for barrier opening in acute conditions, or (2) sprouting of immature blood vessels in chronic conditions such as brain tumors.

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Cerebral Edema

By Oliver Kempski

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CEREBRAL EDEMA HAS long been recognized as a common, sometimes nonspecific finding in a variety of cerebral disorders, in association with toxic, anoxic, and metabolic disturbances, as well as with infections, trauma and tumors. Brain edema is defined as an increase of brain water content which causes an expansion of brain volume.[1] In contrast to many other organs, the increase of brain water content is a serious condition which becomes life threatening if intracranial pressure (ICP) increases because of volume expansion, thereby reducing cerebral perfusion pressure and, hence, cerebral blood flow. Edema is localized either intracellularily (cytotoxic edema) or interstitially (vasogenic edema). Although the 2 types share similar consequences (ICP increase), their pathophysiology is quite different (Table 1). The terms vasogenic and cytotoxic introduced by Klatzo in 1967[2] have greatly advanced our pathophysiologic understanding and remain in use because of their functional significance. Traumatic and ischemic brain edema often present with a mixed morphology which changes during the time course of the primary disease. Additional subtypes of brain edema not covered by Klatzo's definition are interstitial edema found in hydrocephalus patients and edema from systemic osmotic imbalance, eg, found after rapid normalization of plasma hyperosmolarity.

VASOGENIC EDEMA

The Blood-Brain Barrier (BBB)

Vasogenic edema is a consequence of damage to the BBB. The BBB shields brain parenchyma from plasma constituents. In contrast to other tissues, passage of ions and large molecules from plasma to brain is restricted by the BBB. The BBB consists of endothelial cells connected by tight junctions, a basal membrane and surrounding glial endfeet. Barrier function in the healthy brain is a result of tight junctions together with the absence of fenestrated endothelium and vesicular transport. The barrier impedes bulk flow and has high reflection coefficients for electrolytes and other solutes, which, therefore, enter the brain mostly via specific transport systems.[3,4] Water permeability, on the other hand is remarkably high: approximately 50% of all brain water is exchanged by bidirectional diffusion within seconds.[5]

BBB damage may occur from many causes. Traumatic damage as well as mediator substances[6] such as kinins,[7] arachidonic acid,[8] thrombin,[9] histamine,[10] or interleukins[11] may disrupt the morphologic integrity. The mechanisms involved are not fully understood so far. Vast increases of arterial pressure can disturb the barrier, possibly by opening of tight junctions. Rapid infusions of hypertonic solutions cause a shrinkage of endothelial cells, again with opening of tight junctions, and permit temporary passage of plasma constituents into the cerebral parenchyma.[12] Both conditions, however, do not lead to vasogenic edema if there is no additional tissue damage.[13,14] Opening of tight junctions of capillary endothelial cells may experimentally be induced by intracarotid injection of protamine sulfate,[15] which reduces the number of

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Table 1. Characteristics of Vasogenic and Cytotoxic Brain Edema

	Vasogenic	Cytotoxic
Cause	BBB damage: Acute: trauma, stroke, hemorrhage, arterial hypertension Chronic: tumor, abscess, encephalitis	Loss of cell volume regulation either because of pump failure, or result of homeostatic mechanisms regulating the neuronal environment, eg, after ischemia, anoxia, intoxications (hexachlorophene, triethyl tin, dinitrophenol, 6-amino nicotinamide)
BBB permeability	Increased	Unchanged
Edema fluid	Contains macromolecules (plasma filtrate)	Located intracellularly, no plasma filtrate
Morphology	Interstitial localization, expanded extracellular space, white matter most affected, often astrocytic swelling as secondary phenomenon	Swelling of cellular elements: dendrites and astrocytic endfeet; extracellular space reduced

Data from Klatzo.[19]

negatively charged sites along the luminal endothelial membrane.

Brain tumors are surrounded by vasogenic edema which results from sprouting of new, immature blood vessels with an incomplete BBB. Among the mediators involved is probably vascular endothelial growth factor (VEGF) which is also known as vascular permeability factor, and which is far more potent than histamine in inducing capillary permeability.[16] VEGF is indeed found in specimens of human glioma tissue[16,17] as well as brain metastases.[18]

Vasogenic edema fluid is spreading from the site of BBB leakage predominantly via the extracellular space of the white matter. This can be shown experimentally by injecting plasma protein markers at various time points after focal opening of the barrier: the markers immediately after injection are only found at the lesion site and spread with the edema fluid.[2,19] Moreover, some macromolecules also spread intraneuronally from a focus of BBB leakage into remote areas of the central nervous system.[20]

Vasogenic edema fluid apart from plasma proteins contains all other plasma constituents which are normally prevented from entering the cerebral parenchyma. Therefore, those substances can interact with neurons and glia, and impose an additional homeostatic workload, especially to astrocytes. An example is the neurotransmitter glutamate which is present in plasma but virtually absent in the extracellular space of the brain. Glutamate can become neurotoxic under conditions of impaired energy supply, and can aggravate edema if the BBB is disturbed.[21-23]

Biophysics of BBB Opening

The BBB under physiological conditions is quite resistant against bulk flow or fluid uptake into the brain. This is attributable to the high reflection coefficient for electrolytes. Therefore, most water-soluble substances which readily pass the barrier are transported by specific carrier systems. Net transport of fluid from the vasculature across the BBB into brain parenchyma is described as follows[24]:

$$J_v = L_p(P_{capill} - P_{tiss}) - \Sigma\sigma_s(\pi_{capill} - \pi_{tiss})_s$$

J_v=bulk flow,

L_p=hydraulic conductivity for fluid through BBB

P_{capill}, P_{tiss}=hydrostatic pressure (capillaries, tissue)

σ_s=reflexion coefficient for solutes

π_{capill}, π_{tiss}=osmotic pressure (capillaries, tissue)

The formula illustrates that extravasation depends both, on the hydraulic conductivity which is increased after BBB damage, and on the hydrostatic pressure gradient between vasculature and tissue. Hence, vasogenic edema formation will increase during hypertensive events, whereas reduction of systemic blood pressure reduces extravasation.[19]

Spreading and Clearance of Vasogenic Edema

Passage of edema fluid through the parenchyma, white matter in particular, is mainly by bulk flow. Spreading and clearance of vasogenic edema depend on hydrostatic pressure gradients which can be measured between the site of BBB damage and the clearance sites.[25,26] These are located mostly at the interfaces to the cerebrospinal fluid, ie, the ependyma lining the ventricular system of the brain. In addition, components within the edema fluid are removed by phagocytosis and by specific uptake systems. The content of plasma proteins is important for the kinetics of edema clearance. Probably because of their colloid osmotic properties high protein concentrations in the edema fluid prolong the persistence of edema.[27] Large molecules in the edema fluid such as proteins also gain access to the cortical neurophil, where diffusion rather than bulk flow is the major mechanism of spread through the extracellular space.[28]

CYTOTOXIC EDEMA

Cytotoxic edema is characterized by intracellular solute and fluid accumulation from extracellular sources, eg, the extracellular space and the vasculature. The driving force of fluid movement is either a translocation of electrolytes into the cell or the intracellular breakdown of macromolecules to smaller idiogenic osmoles.[29] In global cerebral ischemia both, the generation of idiogenic osmoles, and an influx of mostly Na^+ ions cause the swelling of brain cells with a delay of 2 to 5 minutes after onset of ischemia. Swelling initially is just a translocation of interstitial water into the intracellular compartment, ie, not edema. Only after beginning of recirculation can a net accumulation of fluid occur: the interstitial space recovers its initial size by influx of fluid from the reperfused vasculature, whereas cells remain swollen.[29] In addition, the ischemic brain has become hypertonic because of generation of idiogenic osmoles, and on recirculation fluid moves from the isotonic plasma compartment into the hypertonic brain parenchyma.[29]

Apart from purely osmotic causes, cell swelling in general has been attributed to a failing pump-leak equilibrium.[30] This DONNAN equilibrium model postulates that influx of osmotically active solutes, Na^+ in particular, is counteracted by active, energy requiring pumping. Therefore, swelling of nerve and glial cells can be attributed to failure of active Na^+ export via Na/K-ATPase because of energy shortage, and increase of Na^+ influx because of increased membrane permeability or activation of Na^+-driven ion pumps.

In pathophysiologic conditions associated with cell swelling such as ischemia or hypoxia both conditions are fulfilled. Energy shortage is a direct consequence, whereas membrane permeability for Na^+ ions may increase secondarily because of an extracellular accumulation of excitatory neurotransmitters. Interestingly neither astroglial nor neuronal cells swell in anoxia in vitro as long as all other extracellular conditions are maintained normal, ie, concentrations of transmitters, electrolytes, or pH.[31,32] Glutamate is the most important excitatory transmitter and has a pivotal role in the pathophysiology of cerebral ischemia and trauma.[22,23,33] The interaction of glutamate with a host of glutamate receptors located on the postsynaptic membrane of neurons but also on glial cells is followed by an opening of Na^+ channels, Na^+ influx,[22] and in consequence, swelling.[34]

Other mediator mechanisms are acting via several pathways. Free fatty acids for example are liberated during ischemic episodes,[33] cause glial swelling,[35] and affect membrane transport systems and pH_i regulation.[35]

The term cytotoxic swelling suggests cell swelling in the brain to be always a pathologic process. This is not true and, therefore, misleading. In a series of studies we and others could show that glial cells swell while exerting homeostatic functions such as uptake of glutamate[34,36] or K^+ ions.[37,38] Those homeostatic functions always involve activation of countertransporters which go along with a net movement of ions, mostly Na^+, into the cell and, therefore swelling. Under physiological conditions cell volume is rapidly normalized by active Na^+ extrusion. Only if Na^+/K^+ exchange is compromised in addition will the swelling persist. Best studied so far is astroglial swelling during regulation of intracellular pH.[39,40] Under well-controlled extracellular conditions astrocytes swell as soon as the extracellular pH drops below 6.8.[39,40] Swelling, again, is the result of an activation of ion transport systems: prevention of swelling by specific inhibitors suggests that Na^+/H^+ exchange and Cl^-/HCO_3^--antiports are activated, and cause a net uptake of osmotic activity. The severity of swelling is related to the degree

of acidosis.[40] Interestingly, cell viability does not suffer during acidosis as low as pH_e>6.0.[40]

OTHER TYPES OF EDEMA

Interstitial Edema

Obstructive hydrocephalus results from blockage of cerebrospinal fluid (CSF) reabsorption or efflux. This causes increases of intracranial pressure (ICP) and of cerebral water content in the periventricular white matter because of movement of CSF across the ventricular walls.[41] Edema in this case is located interstitially but, in contrast to vasogenic edema, has the same composition as CSF, and hence has a low protein content.

Edema Resulting From Osmotic Gradients

Acute reductions of intravascular osmolarity go along with water accumulation in brain parenchyma because water can readily pass the BBB. Clinical examples are dialysis accidents, inadequate antidiuretic hormone syndrome, or rapid rehydration of hyperosmolar conditions (severe dehydration, diabetic coma). Edema in this case is a result of osmotic gradients. The BBB is not affected and cytotoxic mechanisms are not involved. To prevent dramatic brain swelling during rehydration of patients, plasma osmolarity should not be reduced more than 1 to 2 mOsm per hour.

THERAPY

Specific therapeutic measures are not at hand so far. Steroids are effective in chronic types of BBB dysfunction only, eg, in brain tumor patients. Therefore, therapy in all other cases is directed against the most severe consequence of cerebral edema, ie, the increase of intracranial pressure. Elevated ICP can be temporarily reduced by infusions of hypertonic fluid. Mannitol is used in most instances although mannitol may even aggravate edema once it passes the damaged BBB and accumulates in the cerebral parenchyma (rebound effect). Recently, the use of hypertonic saline has been suggested as an alternative.[42] For many years hyperventilation was used to lower ICP because it lowers cerebral blood volume, and thereby ICP. Now it becomes clear that the reduction of cerebral blood flow during hyperventilation may be harmful and oxygenation is not improving.[43,44] Therefore p_aCO_2 should not be reduced below 32mmHg. Most important prerequisite for any successful treatment is a careful ICP monitoring of the patient.

Although the pathophysiology of brain edema has been studied in detail, many open questions remain. The recent discovery of aquaporins in brain[45] in the future may help to better understand this issue: aquaporin-4 (AQP-4) is the major aquaporin found in brain, and it is most abundant in perivascular glial endfeet.[46] AQP-4 knockout mice have recently been shown to have less edema after acute water intoxication or ischemic stroke.[47] These results implicate a key role for AQP-4 in modulating brain water transport, and suggest that AQP-4 inhibition may provide a new therapeutic option for reducing brain edema in a wide variety of cerebral disorders.[47]

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